Medicines in renal disease

After completing this tutorial, you will be able to:

- Make decisions about appropriate choice and dose of medicines in patients with renal impairment.
- Assess and calculate renal function.
- Describe the main types of renal replacement therapy and how they may affect drug therapy.
- Explain three basic mechanisms by which medicines may adversely affect the kidney.

Why this subject matters...

Renal impairment is common in hospitals and pharmacists are often asked to help choose medicines that are safe in these patients, or to advise on dose reduction.

Prescribing in renal failure is not an exact science. The practical knowledge of clinical professionals combined with some published evidence, and the basic principles of drug clearance provide the backbone of information available.

Human kidney cell
Courtesy of Alison Dun, Edinburgh Super-Resolution Imaging Consortium, CC BY 4.0
Drugs eliminated by the kidney

Most systemically administered drugs are eliminated at least partly by the kidney, even if it is only a tiny proportion of the administered dose. However, for some drugs, the kidney is the major site for elimination of unchanged drug and these are particularly liable to require careful dose adjustment in renal dysfunction to prevent accumulation.

Examples of drugs principally eliminated unchanged by the kidney include:

<table>
<thead>
<tr>
<th>Aciclovir</th>
<th>Cefotaxime</th>
<th>Ciprofloxacin</th>
<th>Digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td>Fluconazole</td>
<td>Gentamicin</td>
<td>Lithium</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Methotrexate</td>
<td>Pamidronate</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

In addition, there are drugs with therapeutic activity at least partly dependent upon metabolites that are excreted unchanged by the kidney. An example is allopurinol, which has an active metabolite called oxipurinol which works in the same way as the parent drug. Some drugs have toxic metabolites that are eliminated renally. For example nor-pethidine, a major metabolite of pethidine, can accumulate in renal failure to cause CNS toxicity such as convulsions.

Medicines and the kidneys

The way that a medicine behaves in the body can be strongly influenced by the kidney and any degree of reduced function it has. The kidney affects medicines in three principal ways:

1. **Excretion**
   Reduced renal clearance of drugs in renal impairment is an important factor when considering dosage adjustments. A fall in renal drug clearance usually indicates a reduction in the number of functioning nephrons.

   Apart from the parent drug, many active or toxic drug metabolites depend upon the kidney for elimination. The high incidence of adverse drug reactions seen in patients with renal failure may be explained in part by the accumulation of drugs themselves or their metabolites.

2. **Distribution and bioavailability**
   Renal insufficiency frequently alters the volume of distribution of drugs. Oedema or ascites may increase the apparent volume of distribution of highly water-soluble drugs. Higher doses may be needed to produce the desired therapeutic effect. Conversely dehydration or muscle wasting may result in unexpectedly high plasma concentrations of drugs.

   Predicting the clinical consequences of altered protein binding in renal insufficiency is difficult. Plasma protein binding is decreased when plasma urea levels are high (uraemia).
due to altered albumin affinity for the drug. Patients with chronic kidney disease may also have hypoalbuminaemia. Decreased binding results in more free drug being available at the site of action but a shorter half-life as more free drug can be metabolised and/or excreted.

Patients with uraemia are often more susceptible to drug effects (e.g. increased effect of CNS depressants due to increased permeability of the blood brain barrier).

3. Metabolism

The kidney is a site of metabolism in only two clinically important examples. The conversion of 25-hydroxycholecalciferol to the active form of vitamin D called 1,25-dihydroxycholecalciferol (calcitriol) takes place in the kidney, and this process is often impaired in patients with renal failure.

Patients with renal failure requiring vitamin D supplementation should be given the hydroxylated derivatives: either alfalcaldiol (1-alpha-hydroxycholecalciferol) or calcitriol.

The kidney is also a major site of insulin metabolism and so patients with diabetes and renal failure may require less insulin.
Assessing renal function

The extent of accumulation of drugs in renal impairment depends on the degree of dysfunction, the normal route of excretion, and the dose. Before a drug and dose schedule can be chosen, the severity of renal function must be established. To refresh your memory about how the nephron works, watch this short video.

Renal function is universally assessed by measuring or estimating glomerular filtration rate (GFR), which reflects the number of functioning glomeruli. The GFR can be estimated by looking at the rate at which the body clears one of its own waste products – creatinine. This is called the creatinine clearance (CrCl). Using serum creatinine to calculate CrCl assumes that renal function and serum creatinine are stable.

The creatinine clearance is calculated as follows using the Cockcroft & Gault equation:

\[ \text{CrCl} = F \times (140 - \text{age}) \times \frac{\text{weight in Kg}}{\text{plasma creatinine (micromol/L)}} \]

where \( F = 1.04 \) in females and \( 1.23 \) in males. Weight should be ideal body weight (IBW) particularly in oedematous patients and patients with ascites. For patients who are obese, IBW can be used but some experts have suggested that an adjustment factor of 40% be applied to the patient’s excess weight over their ideal weight. Refer to the Information sources for much more guidance.

The equation should not be used in children, pregnancy, marked catabolism or rapidly changing renal function. Use in patients with muscle wasting diseases will lead to an overestimation of the CrCl.
An alternative method of expressing renal function uses the Modification of Diet in Renal Disease (MDRD) formula to give an estimate of GFR (known as eGFR). There are similarities with the Cockcroft & Gault equation but important differences include the assumption that patients are of average weight and build and so are of average surface area (1.73 square metres).

![Diagram showing 1 = glomerulus; 2 = proximal tubule; 3 = distal tubule](image)

It follows that this method should not be used for patients who are at extremes of weight, are pregnant, or for children. It should also not be used for patients taking drugs with a narrow therapeutic range and requires renal function to have been stable over several days or more.

The MDRD and Cockcroft & Gault equations may produce different estimates of renal function and are not interchangeable. Most published information on drug elimination in renal failure is usually stated in terms of CrCl using the Cockcroft and Gault equation so take care when interpreting such data. The BNF is a notable exception having adopted eGFR for most drugs.

What counts as normal renal function and renal failure depends upon the equation used. Again, refer to the Information sources for more guidance. It is important to remember that the normal process of ageing involves the loss of nephrons and therefore it is reasonable to assume that all elderly patients have some degree of renal impairment.

Plasma urea can be used to estimate renal function but its production is more variable than that of creatinine and is therefore not reliable.
Renal replacement therapy

Renal replacement therapy (RRT) is indicated when renal function is so poor that the kidneys are barely operational. RRT is used in the management of acute kidney injury (AKI) to remove toxins, excess fluid and to correct biochemical disturbances. It also forms part of ongoing regular care in patients with end-stage chronic renal failure where kidneys have ceased to function permanently.

There are four main types of renal replacement therapy (RRT) in common use:

- Haemodialysis (HD)
- Peritoneal dialysis (PD)
- Haemofiltration (HF)
- Haemodiafiltration (HDF)

In HD, blood is presented to one side of a membrane, and a dialysis solution with or without pressure is presented to the other side. This encourages toxins to leave the patient’s blood and enter the solution by diffusion. Fluid is removed by a process called ‘ultrafiltration’. In PD this membrane is the patient’s peritoneum. There are two kinds of PD. Continuous Ambulatory Peritoneal Dialysis (CAPD) involves regularly instilling fluid into the abdomen during the day, and later draining it. Automated Peritoneal Dialysis (APD) is the same basic process except that a machine delivers and then drains the fluid at night while sleeping.

In HF, blood is presented to one side of a membrane, but there is no solution on the other side: pressure is used to pull water and solutes through the membrane and this ‘filtrate’ is then removed. HDF is a hybrid of HD and HF.

HD is performed intermittently (e.g. three times a week) and usually as an outpatient, whereas HF and HDF are continuous processes typically seen in intensive care patients.

A detailed discussion of the differences between techniques is beyond this tutorial, but the diagram on the next page compares the techniques.

NHS Choices has information for patients about dialysis, and you can also see a detailed diagram of a typical method by which haemodialysis is organised on page 8.
<table>
<thead>
<tr>
<th>Uses semi-permeable membrane</th>
<th>Uses highly permeable membrane</th>
<th>Uses permeable membrane that allows diffusion (various techniques are used to achieve this)</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ An intermittent process – e.g. 3 short sessions per week.</td>
<td>➢ Slow flow rate of blood but a continuous, 24 hour, process therefore large volumes of fluid removed.</td>
<td>➢ Adopts elements of dialysis and filtration.</td>
</tr>
<tr>
<td>➢ Fast flow rate using a pump enabling processing of big blood volumes.</td>
<td>➢ Solute removal by filtration (“sieving”).</td>
<td>➢ The membrane allows both dialysis (diffusion) and filtration.</td>
</tr>
<tr>
<td>➢ Rapid clearance of low molecular weight solutes by diffusion. Comparatively little loss of fluid.</td>
<td>➢ Pump not needed if blood is supplied from an artery and feeds back to a vein. A pump is used if blood originates from a vein.</td>
<td>➢ It is a continuous process not intermittent.</td>
</tr>
<tr>
<td>➢ Speed and clearance of solutes determined by molecular size, osmotic pull across membrane and flow rate.</td>
<td>➢ Larger pores in the membrane than in haemodialysis so clears comparatively more medium molecular weight solutes.</td>
<td>➢ Blood is pumped if a venous-venous connection is made, but not if there is an arterio-venous connection (less common).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ It is the most effective at removing solutes.</td>
</tr>
</tbody>
</table>
Organisation of haemodialysis

This illustrates the flow of a patient’s blood through the haemodialysis machine.

Courtesy of Yassine Mrabet, Wikimedia Commons
Drug removal by RRT

Factors affecting the removal of a drug from the blood by RRT include:

- Protein binding – highly protein bound drugs are not generally removed by RRT.
- Molecular weight – very large molecules are less likely to be removed than smaller ones.
- Water solubility – dialysis solutions are aqueous so water-soluble drugs enter them preferentially. Lipid-soluble drugs tend to have bigger volumes of distribution and so concentrations in plasma are comparatively small.
- Flow rate, and the chemistry and surface area of the membrane.

Dose adjustment to allow for RRT is only necessary for drugs that require dose adjustment because of the presence of renal failure. But given the major differences between the forms of RRT, it is vital to know which type a patient is receiving before offering any advice! In general the following basic rules apply:

- No RRT is as effective as the normal kidney – so doses used will never be larger than those recommended in normal renal function.
- Drugs which are cleared by the kidneys are usually dialysed, and vice versa, although there are some anomalies.

If there are no specific guidelines on how to dose a drug in a particular RRT system then for HD and PD use a dose as would be used for a GFR of less than 10mL/min (i.e. severe failure). In practice, although it is recognised that haemofiltration is worse at drug clearance than haemodiafiltration, intensive care units tend to dose patients on either as if they have a GFR of about 15-25 mL/min, i.e. as for moderate renal impairment.
- Always aim to give drugs after any session of HD otherwise the drug could be removed before it has time to act fully. For haemofiltration or haemodiafiltration, since both are continuous processes, there is no need to schedule doses around RRT sessions.
After a renal transplant

Once a kidney transplant has stabilised, patients should ideally have a reasonably healthy GFR of greater than 40mL/min. Consequently, dose reduction of drugs that are renally-eliminated is not usually needed. However, graft function does tend to diminish with time, so it is imperative to check renal function regularly.

Many of the immunosuppressants taken post-transplant interact with a variety of drugs and you should **always check for interactions**. Common immunosuppressants used to prevent transplant rejection include:

<table>
<thead>
<tr>
<th>Ciclosporin</th>
<th>Tacrolimus</th>
<th>Mycophenolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>Azathioprine</td>
<td>Steroids</td>
</tr>
</tbody>
</table>

A transplanted kidney is positioned lower in the pelvis than the patient’s own kidneys and attached to the common iliac artery and vein.


Bear in mind that transplant patients only have one kidney, and it may not have perfect function, so it is vital to avoid all medicines that may impair kidney function (e.g. NSAIDs).
Medicines that impair kidney function

Three common mechanisms of drug-induced renal impairment are:

- Reduced GFR caused by interference with the physiologic function of the kidney (e.g. NSAIDs reduce blood flow through the kidney). This is sometimes called **functional renal impairment** because the physical structure of the kidney is not damaged.

- Physical injury to parts of the kidney (e.g. necrosis of tubules with aminoglycosides). Traditionally, medicines that damage the nephron are termed **nephrotoxic**.

- Immune-based inflammatory reaction within the kidney presenting as **glomerulonephritis** (e.g. penicillins, gold salts).

NHS England’s **Think Kidneys** programme includes **guidelines for medicines optimisation** in patients with acute kidney injury (AKI). This gives advice on managing patients with AKI that may be drug-induced and on medicines that may be harmful in AKI. From this document, medication identified as being especially likely to cause AKI can be remembered using the acronym **CANDA**: Contrast media, **ACE** inhibitors, **NSAIDs**, **Diuretics** and **Angiotensin** receptor blockers.

Drugs that are potentially harmful to the kidney should preferably be avoided in any patients with renal impairment as their renal reserve is less and any ill effects may lead to AKI. In end-stage renal failure, where patients are permanently on dialysis and GFR is typically less than 5mL/min, renal function cannot get any worse so the use of nephrotoxic drugs is acceptable if clinically indicated.

![Scanning electron microscope section of kidney tubule](Courtesy of David Gregory & Debbie Marshall CC BY 4.0)
Suggested questions

They may not apply to every situation you come across, but here are some questions you should be thinking about in practice if asked to advise on dosage or suitability of a medicine in renal dysfunction:

The Medicine

- What is the indication for the drug? In case you have to offer safer alternatives.
- Which agent would you prefer to use, and are there any alternatives you’d consider? This helps you focus on therapeutic alternatives that the prescriber thinks are most appropriate to the patient’s clinical condition or history.

The Patient

- Extent of renal impairment? Calculate the creatinine clearance where necessary, for which you’d need to ask about the age, weight and height of the patient and their serum creatinine.
• Is this acute or chronic impairment? Or is it 'acute on chronic' – someone with pre-existing chronic failure, who has had a sudden drop in function? An acute impairment might require ongoing monitoring and revision of the dose when the impairment starts to improve.

• Is renal function stable? Or is it deteriorating, improving, or fluctuating? This determines whether a dose adjustment that you recommend might need to be revised regularly as renal function changes. A medicine that is largely cleared by non-renal routes is preferable in this situation if possible.

• Which, if any, renal replacement therapy is being used? You need to tailor your dose recommendation to the individual patient’s circumstances. Ask about the timing of any intermittent peritoneal dialysis or haemodialysis because doses may need to be given post-dialysis.

**Going Forward**

• Who needs to know? Who can change therapy or dose if necessary? Will the patient and their GP be informed if dose adjustments will affect care after leaving hospital?

• Who will be monitoring the patient? If renal function changes, it may affect side effects or efficacy.
Information sources

If you have a renal pharmacist in your Trust then ask them for advice about managing any patient where you are not sure.

For straightforward questions about dose adjustment in renal disease, start with the SPC and then the Renal Drug Database. Both of these sources tend to give practical advice on dosing according to the extent of impairment.

The website Think Kidneys is a helpful NHS resource with videos, information leaflets, and other resources for patients and professionals. In the Resources section there are a suite of tools and educational materials aimed at pharmacists. A particularly valuable tool is the Medicines Optimisation Toolkit for Acute Kidney Injury (AKI) which helps you choose and review medicines in these patients.

Martindale (or Micromedex if you have it) can be helpful before you consider undertaking an Embase or Medline search. These searches can be quite difficult to do in practice.

Think about whether there may be expert guidance about the medical condition you have been asked about from a Royal College or other specialist body/hospital. Sometimes their advice will include options for selected groups of patients such as those with renal disease. You may be able to find these through NICE Evidence Search.

For enquiries about drug-induced renal failure, don’t forget all your ADR resources.

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to evaluating websites about medicines.

Presenting your answer

Once you’ve asked sufficient questions, gathered the information required and assessed it, you’ll need to provide an answer. As a reminder, we offer some general guidance on answering clinical problems. You might like to refresh your memory if you’ve not looked at this recently.
Next steps in learning...

Your education as a professional never stops, but here are some suggestions to take you beyond what’s on this site.

If you have an interest in caring for patients with renal disease, then you should consider joining the UK Renal Pharmacy Group. It’s an opportunity to make contact with colleagues with similar interests, share expert resources, receive training, and keep up-to-date. Most of the RPG website is only accessible to members, but the site provides a free beginner’s guide to chronic kidney disease, as well as a Powerpoint download on pharmacokinetics and drug dosing in renal impairment.

CPPE has various learning available on its renal home page including an introduction to renal, a quiz, and core learning on Acute Kidney Injury which aims to raise awareness of the pharmacy team’s potential for preventing acute kidney injury in those at risk.

The Kidn-e Project is a collaboration between the Renal Association, the Royal College of Physicians, and e-Learning for Healthcare. Two interactive case-based modules cover the causes, assessment, diagnosis and management of Acute Kidney Injury and Chronic Kidney Disease.

The Kidn-e programme is available to NHS staff in England via the National Learning Management System which is integrated with the Electronic Staff Record. Your tutor or education & training lead can show you how to access this.

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